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Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension (Review)

Ho MJ, Li ECK, Wright JM

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[Intervention Review]

Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

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ABSTRACT

Background

Blood pressure is a commonly measured risk factor for non-fatal and fatal cardiovascular adverse events such as heart attacks and strokes. Clinical trials have suggested that coenzyme Q10, a non-prescription nutritional supplement, can effectively lower blood pressure (BP). When this review was completed and published in October 2009, it concluded that “due to the possible unreliability of the 3 included studies, it is uncertain whether or not coenzyme Q10 reduces blood pressure in the long-term management of primary hypertension.”

Objectives

To determine the blood pressure lowering effect of coenzyme Q10 in primary hypertension.

Search methods

We searched the Hypertension Group Specialised Register (1946 to November 2015), The Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2015, Issue 10), MEDLINE (1946 to November 2015), MEDLINE In-Process (accessed 10 November 2015), EMBASE (1974 to November 2015), Web of Science (1899 to November 2015), CINAHL (1970 to November 2015), and ClinicalTrials.gov (accessed 10 November 2015). We also searched reference lists of articles for relevant clinical trials in any language.

Selection criteria

Double blind, randomized, placebo-controlled parallel or cross-over trials evaluating the blood pressure (BP) lowering efficacy of coenzyme Q10 for a duration of at least three weeks, in patients with primary hypertension.

Data collection and analysis

The primary author determined trial inclusion, extracted the data and assessed the risk of bias. The second author independently verified trial inclusion and data extraction.

Main results

In this update of the review, one new randomized, controlled cross-over trial with a total of 30 participants was added, and one trial included in the initial review was excluded. Only two of the three included trials were pooled in the meta-analysis, as one trial was judged to have an unacceptably high risk of bias. In the meta-analysis of two RCTs (50 participants), coenzyme Q10 did not significantly change systolic BP: -3.68 mm Hg (95% confidence interval (CI) -8.86 to 1.49), or diastolic BP: -2.03 mm Hg (95% CI -4.86 to 0.81]), based on clinic data.

Authors' conclusions

This review provides moderate-quality evidence that coenzyme Q10 does not have a clinically significant effect on blood pressure. In one of three trials reporting adverse effects, coenzyme Q10 was well tolerated. Due to the small number of individuals and studies available for analysis, more well-conducted trials are needed.

PLAIN LANGUAGE SUMMARY

Coenzyme Q10 for High Blood Pressure

Background

High blood pressure is a common condition that can increase risk for certain diseases such as heart attacks, strokes, and kidney disease. Coenzyme Q10, a non-prescription nutritional supplement, has been suggested as a potential drug to lower blood pressure. When this review was completed and published in October 2009, it concluded that "due to the possible unreliability of the three included studies, it is uncertain whether or not coenzyme Q10 reduces blood pressure in the long-term management of primary hypertension."

Review Question

We asked whether coenzyme Q10 compared to a placebo affected blood pressure in patients with high blood pressure.

Study Characteristics

For this update, databases of registered clinical trials and published trial reports were searched up until 10 November 2015 for any studies that tested the effects of coenzyme Q10 on patients' blood pressure. One new trial was found and one trial in the initial review was excluded. These studies measured the effects of coenzyme Q10 on blood pressure in non-hospitalized men and women who took the drugs for 8 to 12 weeks. One of the three trials was judged to have an unacceptably high risk of bias and was not included in the pooled analysis. The total number of patients studied in the two pooled trials was 50.

Key Results

Pooled data from two trials showed that coenzyme Q10 did not affect blood pressure compared to placebo. The number of patients stopping the drug due to adverse effects was also an outcome of interest. In one of the three included trials, coenzyme Q10 was well-tolerated and no adverse effects were reported.

Quality of the Evidence

This review provides moderate-quality evidence that coenzyme Q10 does not lower blood pressure. However, more well-conducted studies are needed to be sure.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Coenzyme Q10 compared with placebo for primary hypertension

Patient population: patients with primary hypertension
Settings: primary care in Japan and New Zealand
Intervention: coenzyme Q10 100 to 200 mg daily
Comparison: placebo

Outcomes	Mean difference in BP mmHg [95% CI]	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
End of treatment SBP (over 12 weeks)	-3.7 mm Hg (-8.9 to 1.5)	50 (2)	⊕⊕⊕○ **moderate**[1]	
End of treatment DBP (over 12 weeks)	-2.0 mm Hg (-4.8 to 0.8)	50 (2)	⊕⊕⊕○ **moderate**[1]	
Withdrawals due to adverse effects		30 (1)		Effect estimate not available; only one study reported this outcome but had no events in either study arm

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Downgraded due to large confidence intervals from a small sample size and small number of included studies.

BACKGROUND

Description of the condition

Hypertension is a common medical condition and major risk factor for stroke, myocardial infarction, congestive heart failure, kidney failure, and peripheral vascular disease. Pharmacological interventions have been shown to reduce blood pressure and modestly decrease stroke, myocardial infarction, and mortality (Musini 2009a). However, hypertension remains prevalent in the community and additional treatment options are needed (Burt 1995).

Description of the intervention

Coenzyme Q10 (CoQ10) is a non-prescription nutritional supplement that is commonly taken daily. Also called ubiquinone, it is a fat soluble molecule that acts as an electron carrier in mitochondria and as a coenzyme for mitochondrial enzymes (Langsjoen 1985). As a bioenergetic molecule, coenzyme Q10 is obtained through both tissue synthesis and diet (Langsjoen 1985). Supplementary oral administration of coenzyme Q10 has been shown to increase coenzyme Q10 levels in plasma, platelets, and white blood cells (Niklowitz 2007).

Studies suggest that CoQ10 deficiency may be associated with a multitude of diseases as diverse as coronary artery disease and congestive heart failure, Parkinson's disease, diabetes, and breast cancer, as well as the risk factor, hypertension (Niklowitz 2007). It has been suggested that CoQ10 has the potential to lower blood pressure without significant adverse events in hypertensive patients (Rosenfeldt 2007).

How the intervention might work

Coenzyme Q10, as an antioxidant, could act directly on vascular endothelium to decrease total peripheral resistance or could act by reducing superoxide synthesis (McCarty 1999). Coenzyme Q10 also has possible anti-atherogenic effects as a modulator of ß-integrin levels on the surface of blood monocytes (Quinzii 2007).

Why it is important to do this review

Many people take CoQ10 for hypertension, cardiovascular health, or both. A non-Cochrane review concluded that CoQ10 reduced blood pressure (Rosenfeldt 2007). However, in that review, there was no reported assessment of the risk of bias in the included trials. The first version of this review was completed and published in October 2009, and concluded that "due to the possible unreliability of the three included studies, it is uncertain whether or not CoQ10 reduces blood pressure in the long-term management of primary hypertension" (Ho 2009). The present update of this systematic review uses the latest Cochrane methodology to assess the blood pressure lowering effect of different doses of CoQ10. The information derived from this review should assist clinicians in determining whether or not it is worth trying CoQ10 as a therapeutic intervention to lower blood pressure, and to help determine whether further studies that measure cardiovascular outcomes should be conducted.

OBJECTIVES

Primary objective:

1. To determine the dose-related effect of coenzyme Q10 on systolic and diastolic blood pressure in hypertensive patients.

Secondary objectives:

1. To determine the dose-related effects of coenzyme Q10 on heart rate.
2. To determine the effects of coenzyme Q10 in different doses on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included study designs that met the following criteria: randomized, placebo-controlled parallel or cross-over trial; double blind; treatment duration of at least three weeks; washout period of at least two weeks before the start of trial or between treatment periods; blood pressure measurement at baseline (following washout) and at one or more time points between 3 to 12 weeks after starting treatment. A washout period of at least two weeks is important, to be reasonably sure that the blood pressure is elevated and stable and that there are no longer any effects of antihypertensive drugs that have been stopped.

Types of participants

We included participants with a baseline systolic blood pressure (SBP) of at least 140 mm Hg or a diastolic blood pressure (DBP) of at least 90 mm Hg, measured in a standard way. We excluded patients with significant renal insufficiency and a documented serum creatinine level greater than 1.5 times the normal values.

We did not restrict participants by age, gender, baseline risk, or other co-morbid conditions.

Types of interventions

Intervention: Coenzyme Q10 (CoQ10) in any dose, as either the sole anti-hypertensive therapy or added to the participants' current anti-hypertensive medication regimen that remained unchanged throughout the study. Data from trials in which CoQ10 titration to a higher dose was based on blood pressure response were not eligible.
Control: Placebo.

Types of outcome measures

Primary outcomes

Change in systolic and diastolic blood pressure from baseline, or difference in endpoint (end-of-treatment) systolic and diastolic blood pressure. Both were considered acceptable outcomes, but if possible, end-of-treatment SBP and DBP values were preferred over change in baseline results. If blood pressure measurements were available at more than one time within the acceptable window, the means of blood pressures taken in the 3 to 12 week range were used.

Secondary outcomes

1. Change in heart rate from baseline or endpoint heart rate.
2. Number of patient withdrawals due to adverse effects.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for primary studies: the Hypertension Group Specialised Register (1946 to November 2015), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2015, Issue 10), MEDLINE (1946 to November 2015), MEDLINE In-Process (accessed 10 November 2015), EMBASE (1974 to November 2015), Web of Science (1899 to November 2015), CINAHL (1970 to November 2015), and ClinicalTrials.gov (accessed 10 November 2015).
We searched electronic databases using a strategy that combined a variation of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to coenzyme Q10 and hypertension. We used no language restrictions. We adapted the MEDLINE search strategy (Appendix 1) for the Hypertension Group Specialised Register (Appendix 2), CENTRAL (Appendix 3), EMBASE (Appendix 4), CINAHL (Appendix 5), and Web of Science (Appendix 6),using the appropriate controlled vocabulary as indicated.

Searching other resources

a) Reference lists of relevant studies and reviews.
b) Contact authors of trials to ask if they know of any unpublished trial reports.

Data collection and analysis

Selection of studies

During the initial screen for potential relevance, we excluded articles whose titles, abstracts, or both, were clearly irrelevant. We retrieved the full text of the remaining articles, and translated them into English where required. We searched the bibliographies of pertinent articles, reviews, and texts for additional citations. Two review authors independently assessed the eligibility of the trials, using a trial selection form. A third review author resolved discrepancies.

Data extraction and management

Two review authors independently extracted data using a standard form, and then cross-checked the data. A second person confirmed all numeric calculations and graphic interpolations.
The position of the patient during blood pressure measurement may affect the blood pressure lowering effect. However, in order not to lose valuable data if only one position was reported, we used data from that position. When blood pressure measurement data were available in more than one position, our first preference was the sitting blood pressure. If standing and supine blood pressures were available, we used standing blood pressure.

Assessment of risk of bias in included studies

We assessed all trials using the 'Risk of bias' tool under the categories: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. For other biases, we considered: patient selection bias, bias specific to the way cross-over trials were reported, and suspected bias due to unrealistic standard deviations.

Measures of treatment effect

We calculated mean differences, using generic inverse variance for the continuous variables systolic and diastolic blood pressure, and heart rate.

Unit of analysis issues

We only accepted cross-over trials for data entry if paired analyses from both periods were reported. Data were entered using generic inverse variance and mean difference for continuous data.

Dealing with missing data

In case of missing information in the included studies, we contacted investigators (using email, letter, fax, or a combination) to obtain the missing information.

We calculated standard errors from the standard deviations in the reported data. In the case of a missing standard deviation and standard error in a study, we imputed the standard deviation, based on the information in the same trial or from other trials using the same dose. We used the following hierarchy (listed from high to low preference) to impute standard deviation values (Heran 2008a; Heran 2008b; Heran 2012; Musini 2008):

1. standard deviation of change in blood pressure from a different position than that of the blood pressure data used.
2. standard deviation of blood pressure at the end of treatment.
3. standard deviation of blood pressure at the end of treatment, measured from a different position than that of the blood pressure data used.
4. standard deviation of blood pressure at baseline (unless this measure was used for entry criteria).
5. mean standard deviation of change in blood pressure from other trials using the same drug and dose.

Assessment of heterogeneity

We used Chi² and I² statistics to test for heterogeneity of treatment effect between the trials. In the event of significant heterogeneity, we used the random-effects model to test for significance. Our preferred method to report the summary statistics of pooled trials was the fixed-effect model.

Data synthesis

We used the Cochrane Review Manager software, RevMan 5.3.5 for data synthesis and analyses.

We pooled the data for the continuous variables of blood pressure and heart rate, measured at three weeks or more after randomization, using the generic inverse variance fixed-effect model for mean differences. Using this method allowed us to pool the results of cross-over and parallel trials. Results from different doses or dosing regimens were pooled due to the paucity of data. The drop-outs due to adverse effects would have been analyzed using relative risk, risk difference, and number needed to harm. However, there was insufficient information in the included studies for this analysis.

Subgroup analysis and investigation of heterogeneity

It was not possible to do the following planned analyses due to the small number of included trials:

1. Trials that were industry-sponsored versus non-industry sponsored trials.
2. Trials with blood pressure data measured in the sitting position versus other measurement positions.
3. Trials with published standard deviations of blood pressure change versus imputed standard deviations.

Sensitivity analysis

The impact of bias on the results was assessed by removing poor quality trials (those with a high risk of bias).

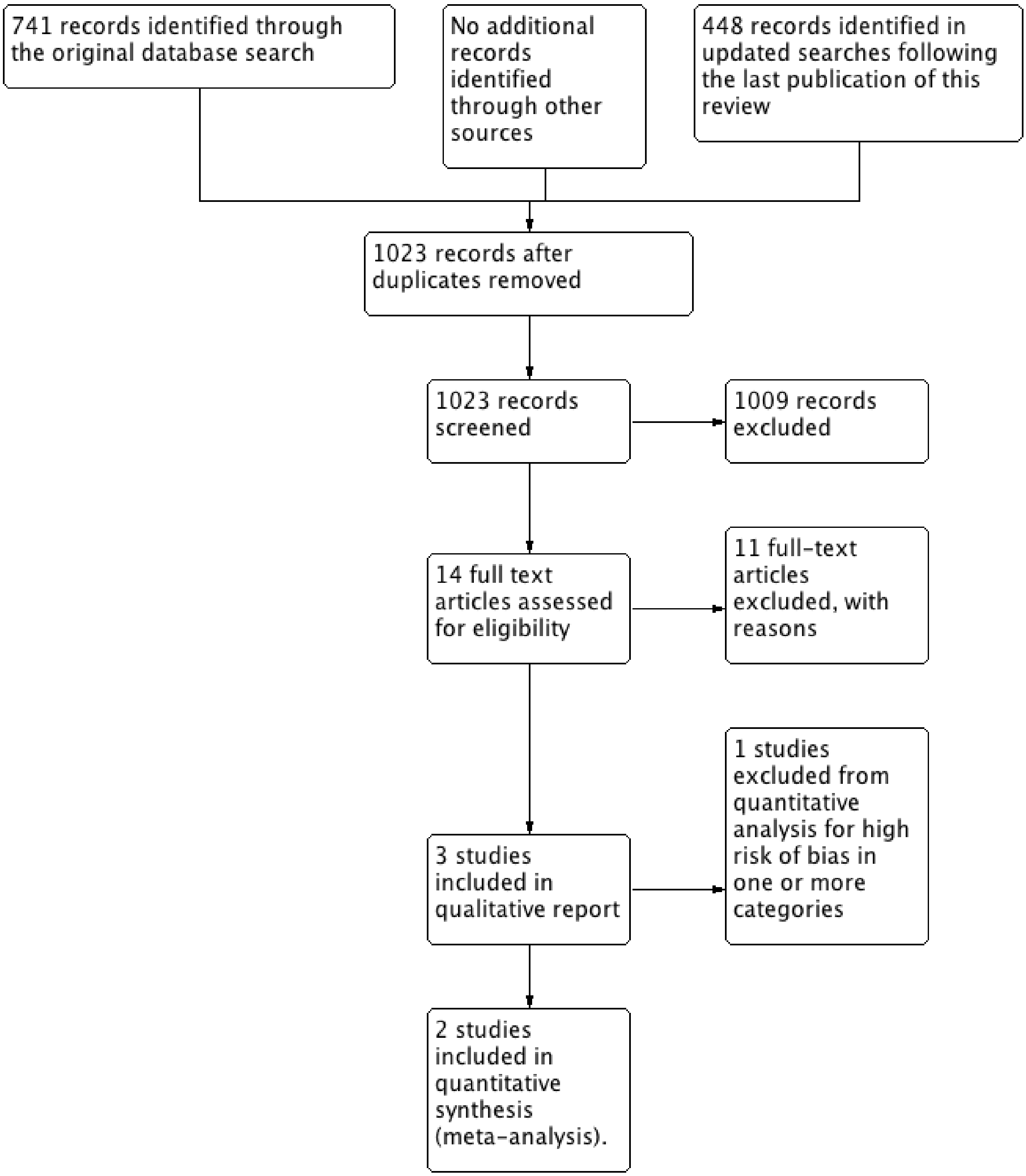
R E S U L T S

Description of studies

Results of the search

See PRISMA flow diagram (Figure 1) for details.

Figure 1. PRISMA Study flow diagram



We identified 741 records in the initial search; 448 more were identified in the updated searches. Of these references, 14 appeared to meet our eligibility criteria; we excluded 11 after screening the full text, one of which had been incorrectly included in the initial review (Singh 1999). Three studies are included in the qualitative report (Digiesi 1990; Yamagami 1986; Young 2012), and two are included in the meta-analysis (Yamagami 1986; Young 2012). Digiesi 1990 was not included in the meta-analysis because we judged it to have an unacceptably high overall risk of bias.

Included studies

See Characteristics of included studies for details.

We described three studies in the 'Characteristics of included studies' table. Only two studies, conducted in Japan and New Zealand, respectively, were included in the meta-analysis (Yamagami 1986; Young 2012). Included participants had an initial blood pressure (BP) higher than 140/90 mm Hg (or at least 130 mm Hg for patients with type 2 diabetes mellitus) in Young 2012, while the participants in Yamagami 1986 had a higher initial BP of at least 150/90 mm Hg. The age of participants ranged from late fifties to early sixties. Young 2012 included participants with metabolic syndrome, while baseline comorbidity data were not available for Yamagami 1986. Yamagami 1986 only included participants with a low CoQ10 level, a low succinate dehydrogenase activity, or both, at baseline. Both trials allowed participants to continue previous anti-hypertensive therapies, but Young 2012 reported exclusion of participants who were previously taking CoQ10. Young 2012 was a cross-over trial with a four-week washout period between two 12-week treatment periods, whereas Yamagami 1986 compared CoQ10 to placebo in a parallel, double blind, randomized controlled trial after a minimum four-week washout period. Yamagami 1986 used 100 mg of CoQ10 daily, while Young 2012 used 100 mg twice daily. Clinic BP data were available for both studies, but Young 2012 also reported 24-hour ambulatory BP monitoring data.

We judged the third included study to have an unacceptably high risk of bias and flaws in study conduct and analysis and thus, we did not include its data in the data analysis for this review (Digiesi 1990). This study was a cross-over trial with a two-week washout period before each 10-week treatment period of 100 mg CoQ10 daily. The problems with the Digiesi 1990 cross-over study are as follows and are also described in the 'Risk of bias' section below. We decided not to pool the data from this trial because we assessed it to be at high risk of bias for allocation concealment, blinding, smaller than expected BP standard deviations, the lack of BP decrease in the placebo group, and the fact that despite it being a paired comparison, it did not report a paired analysis.

Excluded studies

See Characteristics of excluded studies.

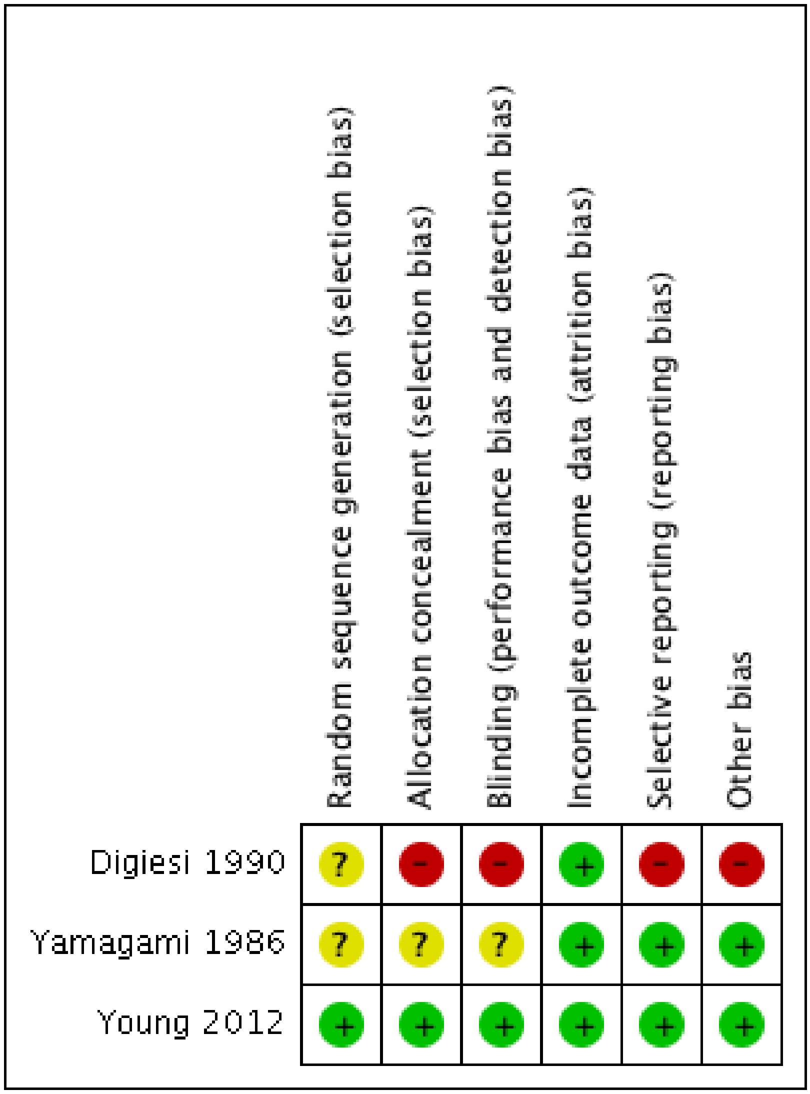
Eleven studies seemed to meet our criteria on abstract screening, but were later excluded after examining the full text. The reasons for exclusion were: lack of randomization (Hata 1977), lack of a placebo control (Digiesi 1994; Drzewoski 1981; Folkers 1981; Langsjoen 1994; Shcherbakova 2010), washout period less than two weeks (Burke 2001), treatment period less than three weeks (Shah 2007), and lack of hypertensive participants in the sample size (Hodgson 2002). We were unable to consider Eghtesadi 2012 further at this time due to the unavailability of a full-text report.

We included Singh 1999 in the initial review but excluded it here, because after reading it carefully again and assessing it with the new 'Risk of bias' criteria, we felt it did not meet our inclusion criteria. It did not describe the sequence generation or allocation concealment processes; subjects in the two groups met separately, suggesting that the blinding integrity was lost; drop-outs after randomization were not described; the doses of other anti-hypertensives were changed during the trial; and BP standard deviations (CoQ10 8.4/4.2 mm Hg, placebo 8.4/4.7 mm Hg) were lower than the average resting BP standard deviation of 14/8 mm Hg seen in other research settings (Musini 2009b; Musini 2014).

Risk of bias in included studies

See risk of bias summary (Figure 2) and Characteristics of included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

One trial described the sequence generation process as using a computer-generated randomization list in blocks of six, a process done by a statistician not clinically involved in the study (Young 2012). The other two trials did not describe the sequence generation process or how allocation concealment was achieved (Digiesi 1990; Yamagami 1986)

Blinding

All trials reported that personnel were blinded, however, only one described a process that would indicate this was definitely the case, i.e. using identical CoQ10 and placebo capsules in identical numbered bottles that were sequentially dispensed by an independent pharmacist (Young 2012). One study described the process as using numbered capsules and locked key codes, but did not report who performed the blinding or whether the capsules were numbered randomly or sequentially (Yamagami 1986). The third study provided no details of blinding (Digiesi 1990).

Incomplete outcome data

Yamagami 1986 and Digiesi 1990 did not lose any subjects to follow-up. Young 2012 did not lose any patients to follow-up either, but one patient in the study had a change in their BP medications in the first treatment phase and was withdrawn from the study.

Selective reporting

Blood pressure data were reported in all trials. Withdrawals due to adverse effects were only reported in Young 2012. They also measured “safety markers, including electrolytes, plasma glucose, renal and liver function, hemoglobin A1c and a full blood count... Urine concentrations of creatinine and sodium were also determined.” Neither Yamagami 1986 nor Digiesi 1990 mentioned any drug adverse effects leading to withdrawal.

Other potential sources of bias

Yamagami 1986 did not provide any details about how they measured blood pressures.

Young 2012 reported that they measured clinic BPs using standard sphygmomanometry between 0700 and 1100h “according to current guideline recommendations.” They described assessing BP “after five minutes of rest in the sitting position using appropriately sized cuffs. Three BP measurements were obtained at two-minute intervals and the mean of these recordings were calculated as the final clinic BP.” These “serial BP measurements were performed by the same trained operator using the same calibrated sphygmomanometer throughout the study.” However, they did not specify which arm was used to measure BP, and whether that same arm was used consistently throughout the study. The American Heart Association 2005 Recommendations (Pickering 2005) that were cited by Young 2012, recommended that “blood pressure should be checked in both arms at the first examination. When there is a consistent interarm difference, the arm with the higher pressure should be used.” If there was not a consistent interarm difference at the initial visit, Young 2012 did not specify which arm they chose, and whether the same one was used throughout the study. Their other cited European Recommendations (O’Brien 2005) only specify bilateral measurement on the initial study and referral to a cardiovascular centre if the systolic or diastolic BPs differ by more than 20 or 10 mm Hg respectively.

Digiesi 1990 used the mean of five BP readings, measured successively every minute. Standard deviations (10/5 mm Hg) were lower than the average resting BP standard deviations (14/8 mm Hg) in similar research settings (Musini 2009b; Musini 2014), and there was no BP decrease in the placebo group, which would be expected from similar research studies (Heran 2008a). Digiesi 1990 was a cross-over trial and did not report the findings as a paired analysis.

Effects of interventions

See: **Summary of findings for the main comparison**

Change in blood pressure (BP) - clinic data

The pooled results of Young 2012 and Yamagami 1986, showed that CoQ10 did not result in a statistically or clinically significant reduction in systolic BP: -3.68 mm Hg (95% confidence interval (CI) -8.86 to 1.49) or diastolic BP: -2.03 mm Hg (95% CI -4.86 to 0.81) compared to placebo (Analysis 1.1; Analysis 1.2; Figure 3; Figure 4).

Figure 3. Forest plot of comparison: 1 Coenzyme Q10 vs Placebo: Clinic data, outcome: 1.1 Mean difference in SBP.

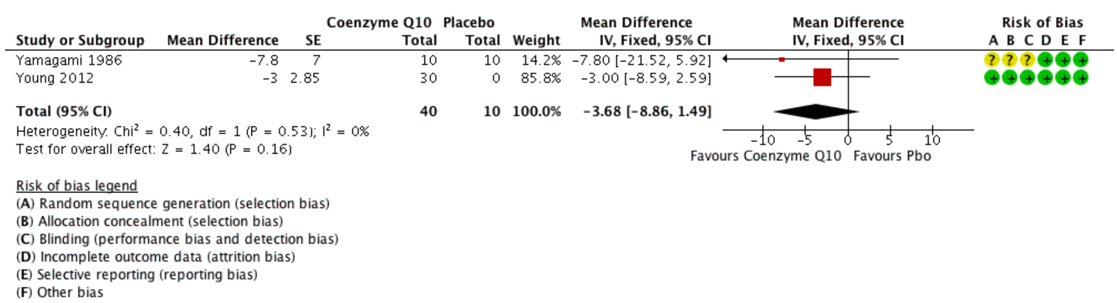
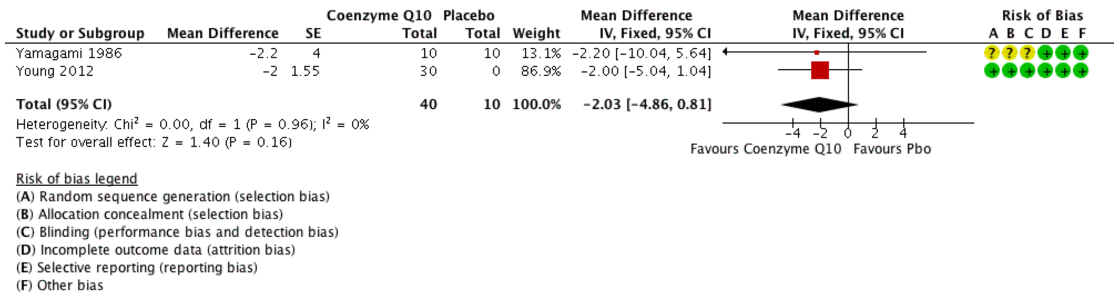


Figure 4. Forest plot of comparison: 1 Coenzyme Q10 vs Placebo: Clinic data, outcome: 1.2 Mean difference in DBP.



Change in heart rate - clinic data

In Young 2012, CoQ10 significantly reduced heart rate by -4.80 beats per minute (95% CI -9.31 to 0.29) compared to placebo, but this was predominantly due to an increase in heart rate in the placebo group, and is unlikely due to an effect of CoQ10 (Analysis 1.3).

Change in blood pressure (BP) and heart rate - 24-hour data

We found no effect of CoQ10 on blood pressure or heart rate compared to placebo in 24-hour ambulatory measurements in Young 2012 (Analysis 2.1; Analysis 2.2; Analysis 2.3).

Withdrawals due to adverse effects

When reported, withdrawals due to adverse effects were not reported by treatment group, so this outcome could not be analyzed in this review.

DISCUSSION

Summary of main results

Please see Summary of findings for the main comparison for details.

This systematic review of coenzyme Q10 (CoQ10) showed no significant decrease in systolic blood pressure (SBP) or diastolic blood pressure (DBP) after 12 weeks of therapy compared to placebo control, based on two RCTs (Figure 2). This finding contrasts with the meta-analysis of the initial Cochrane review of this question, which suggested a clinically significant reduction in BP with CoQ10 (Ho 2009). However, in that review, we were sceptical of the findings because of the very low-quality and high or unclear risk of bias in those RCTs. If we had included Digiesi 1990 in the meta-analysis for this updated review, a small but statistically significant blood pressure lowering effect of CoQ10 would have been found. Yet it is well established that if randomization, concealment of allocation, and blinding are not performed correctly, the effect size is exaggerated. In addition to the biases identified by the risk of bias tool, Digiesi 1990 also reported lower blood pressure standard deviations than expected, which also shed suspicion on the reliability of the results (see the above paragraph in Included studies describing the problems with the Digiesi 1990 trial). Therefore, our judgement was that the high risk of bias of Digiesi 1990 would make the estimate of treatment effect unreliable, and therefore, we did not include this study in the data analysis.

Singh 1999 was included in the initial review but excluded from this review because changes in other anti-hypertensive drugs were allowed and occurred during the trial, and we judged it to be highly unlikely to be a blinded trial. The reliability of the data from the Singh 1999 trial was also questionable, given the investigations into scientific misconduct of the first author, Dr. Singh (White 2005). Singh has been investigated by the BMJ and Lancet (Mann 2005), which have published "expressions of concern" about his work.

Given the lack of effect of CoQ10 on blood pressure after pooling the data from the two higher quality trials (Yamagami 1986; Young 2012), we believe that CoQ10 probably does not have a true BP lowering effect. However, this conclusion suffers from imprecision because it is based on two small RCTs (N = 50), which is why we have downgraded the quality of the evidence that CoQ10 does not affect BP to moderate. Data from more well-conducted RCTs are still needed to address this imprecision. In addition, we would like to be able to add other RCTs addressing this question to our review, which may not have been published in the past because they did not show a significant effect.

The additional findings from Young 2012, showing no effect of CoQ10 on the 24-hour ambulatory monitoring SBP, DBP, or heart rate compared to placebo provide supporting evidence for the conclusion that CoQ10 has no clinically significant effect on BP. The 24-hour measurements are done using an automatic machine, and thus are free from observer bias that could occur with clinic measurements done by a physician or nurse.

Coenzyme Q10 appears to be safe, as none of the three included RCTs reported any significant adverse effects associated with it. Young 2012 reported that "coenzyme Q10 was well tolerated and there were no reported serious adverse effects." There were also "no clinically or statistically significant changes in biochemistry and hematology safety parameters." Yamagami 1986 and Digiesi 1990 did not address this outcome.

Overall completeness and applicability of evidence

In this review, the results of only two RCTs with 50 patients were available for meta-analysis, representing a small number of participants. Young 2012 is the first published RCT of CoQ10 done in hypertensive patients in which there was no trend towards a BP lowering effect. It is probable that there are other RCTs assessing the BP lowering effect of CoQ10 that also showed no effect on blood pressure and were never published. Therefore, it is likely that this review is an incomplete reflection of the totality of available evidence. Hopefully, the publication of the Young 2012 trial and this updated review will encourage individuals who have unpublished negative studies to send them to us or submit them for publication. As evidenced by the Young 2012 publication in the American Journal of Hypertension, publishing trials showing no effect is easier now than it has been in the past.

A possible limitation of this review is that the Young 2012 trial defined hypertension in patients with type 2 diabetes mellitus as SBP at least 130 mm Hg, so that some patients with a SBP lower than 140 mm Hg were likely included. However, this definition of hypertension is consistent with recent practice standards and treatment goals for hypertension in this subset of patients (CHEP 2015), and it is unlikely that inclusion of these patients would affect the results and conclusions.

Quality of the evidence

Interpretation of the findings of this review was difficult because of the substantial bias in some of the available published trials. This problem is a common challenge for many reviews, and was dealt with in this review by not including data for the meta-analysis from the trial that was judged to have an unacceptably high risk of bias (Digiesi 1990).

Agreements and disagreements with other studies or reviews

The conclusions of this review differ from previous systematic reviews looking at the blood pressure lowering effect of CoQ10 in people with hypertension (Rosendfeldt 2003; Rosenfeldt 2007), as well as the initial version of this Cochrane review (Ho 2009). The Rosenfeldt reviews suffer from all the same limitations of the initial Cochrane review, namely that most of the available trials have a high risk of bias. The Rosenfeldt 2007 review also included open label studies, which suffer from a high risk of bias due to lack of blinding. The initial Cochrane review identified the same three RCTs that were identified in the Rosenfeldt reviews (Ho 2009) .

AUTHORS' CONCLUSIONS

Implications for practice

This review provides moderate-quality evidence that coenzyme Q10 does not have a clinically significant effect on blood pressure or heart rate.

Implications for research

As the number of randomized control studies (RCTs) and patients studied is small, more well conducted RCTs are needed to be certain that coenzyme Q10 does not have a clinically important effect on BP and heart rate. In addition to conducting new studies, this could be most readily achieved by ensuring the publication of all RCTs that have been conducted.

ACKNOWLEDGEMENTS

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The authors would like to acknowledge the contribution of Anthony Bellusci, co-author on a previous version of this review, who assisted in identifying trials for the initial published review, independently assessed studies for inclusion, and independently extracted data.

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Young 2012 ***{published data only}***
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Digiesi 1990

Methods	Randomized, placebo-controlled, cross-over trial. 2 week washout period, 10 week treatment period, 2 week treatment suspension, 10 week cross-over treatment
Participants	18 patients (4 women, 14 men) with essential hypertension, WHO stages 1 and 2, average age 55.9 years (range 42 to 66 years). Patients older than 70 years, renal failure or body weight > 90 kg excluded
Interventions	Intervention: Monotherapy with 100 mg oral coenzyme Q10 daily for 10 weeks Control: Placebo
Outcomes	Resting supine SBP and DBP at 10 weeks
Notes	Sources of funding not stated. Small study size.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "...patients were randomly assigned. .. then each patient in group A crossed over to placebo treatment and each patient in group B crossed over to CoQ treatment..." Does not describe the sequence generation process.
Allocation concealment (selection bias)	High risk	Insufficient information provided. Does not describe how allocation concealment was ensured
Blinding (performance bias and detection bias) Blood Pressure	High risk	No information provided as to whether blinding was achieved.
Incomplete outcome data (attrition bias) Blood Pressure	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	BP reported was stated as end of treatment. BPs at other times were not reported
Other bias	High risk	No indication as to how patients were selected, "eighteen subjects were selected from among those presenting with essential

Digiesi 1990 (*Continued*)

		arterial hypertension," so they could have been selected based on previous response to CoQ10 BP standard deviations are lower and not as variable as would be expected

Yamagami 1986

Methods	Randomized, placebo-controlled, double blind trial. Washout period of 4 weeks or more with stable baseline BP. Measurement every 2 weeks for 12 weeks
Participants	52 patients with essential hypertension (BP > 150/90 mm Hg) were selected at random from the outpatient clinic of The Center for Adult Diseases in Osaka, Japan 20 patients (8 men and 12 women, mean age 60 years) with low CoQ10 and low SDH-Q reductase activity were accepted. Conventional hypertension therapies were continued without change
Interventions	Intervention: Monotherapy with 33.3 mg CoQ10 3x daily (100 mg/day) Control: Placebo
Outcomes	SBP and DBP at 2 week intervals (no description of position of patient or method of BP measurement)
Notes	Sources of funding not stated. Limited to patients with low CoQ10 levels, who could be particularly responsive to BP lowering effect of intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 20 patients was randomized..." Does not describe the sequence generation process.
Allocation concealment (selection bias)	Unclear risk	"The capsules were numbered and the code was kept... until all trial had been over." Not clear whether numbers were random or in sequence
Blinding (performance bias and detection bias) Blood Pressure	Unclear risk	Quote [direct quotation, note typographical errors]: "The capsules were numbered and the code was kept... until all trial had been over... After all data were fixed in each case, key code was opened and the change of blood pressure was compared between

Yamagami 1986 *(Continued)*

		coQ group and placebo group." Comment: insufficient information about how key codes were assigned
Incomplete outcome data (attrition bias) Blood Pressure	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	BP data at all time points was provided.
Other bias	Low risk	SD data is as would be expected.

Young 2012

Methods	Randomized, placebo-controlled, double blind cross-over trial
Participants	30 patients (15 men, 15 women) with metabolic syndrome and inadequate BP control (SBP $\geq$ 140 or $\geq$ 130 for patients with type 2 diabetes) on an unchanged, anti-hypertensive regimen. Patients with significant comorbidities (cardiovascular, renal, hepatic, metabolic, etc.) were excluded
Interventions	Cross-over with CoQ10 (100 mg BID) and placebo added to current, unchanged, conventional hypertensive regimen. Patients taking antioxidant vitamin supplementation, including CoQ10, before the trial were excluded (no washout period). A washout period of 4 weeks was present between treatment periods
Outcomes	Mean 24-hour ambulatory SBP and DBP, MAP, pulse pressure, HR, mean daytime and nighttime BP and HR, clinic BP (sitting, mean of 3 measurements after 5 minutes of rest) and HR, plasma CoQ10 levels
Notes	Compliance, safety data and adverse events also documented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed in permutation blocks of six from a computer-generated randomization list by a statistician with no clinical involvement in the study."
Allocation concealment (selection bias)	Low risk	"The study treatments were dispensed by an independent pharmacist in identical numbered bottles with the lowest available number allocated to each sequential participant."

Young 2012 *(Continued)*

Blinding (performance bias and detection bias) Blood Pressure	Low risk	"Participants and investigators administering the treatment and assessing outcomes were blinded to treatment assignment and to plasma coenzyme Q10 levels." "Both Q-Gel and placebo were supplied by Tishcon (Salisbury, MD), and were identical in appearance and taste."
Incomplete outcome data (attrition bias) Blood Pressure	Low risk	The authors performed a modified intention-to-treat analysis: "Of 60 potential participants screened, 31 entered and 30 completed the study and were included in the analysis." The reason for withdrawal from the study of the 1 study participant was obtained by electronic communication from the study authors - the patient had an increase in BP medication during the study
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were reported.
Other bias	Low risk	Research was supported by a grant from the National Heart Foundation of New Zealand (Grant Number 1155). Coenzyme Q10 (Q-Gel) and placebo capsules were supplied by Tishcon, Salisbury, MD. Authors declared no conflicts of interest

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Burke 2001	Washout period was only 10 days.
Digiesi 1994	No placebo control.
Drzewoski 1981	No placebo control.
Eghtesadi 2012	Only an abstract available
Folkers 1981	No placebo control.
Hata 1977	Trial is not randomized, no parallel placebo group. Washout period is only 1 to 2 weeks

(*Continued*)

Hodgson 2002	Included mostly patients with normal blood pressure, baseline BP ranged from 127/75 to 136/80 mm Hg and therefore, did not meet hypertension criteria
Langsjoen 1994	No placebo control.
Shah 2007	Treatment period was less than 3 weeks (longest post-dose period was 8 hours)
Shcherbakova 2010	Not a placebo controlled trial
Singh 1999	Not likely a double blinded trial as different treatment groups met separately. Changes in antihypertensive medications were allowed and occurred during the trial

DATA AND ANALYSES

Comparison 1. Coenzyme Q10 vs Placebo: Clinic data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean difference in SBP	2	50	Mean Difference (Fixed, 95% CI)	-3.68 [-8.86, 1.49]
2 Mean difference in DBP	2	50	Mean Difference (Fixed, 95% CI)	-2.03 [-4.86, 0.81]
3 Mean difference in HR	1		Mean Difference (Fixed, 95% CI)	Subtotals only

Comparison 2. Coenzyme Q10 vs Placebo: 24 hr BP measurements

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean Difference in SBP	1		Mean Difference (Fixed, 95% CI)	Subtotals only
2 Mean Difference in DBP	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3 Mean Difference in HR	1		Mean Difference (Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Coenzyme Q10 vs Placebo: Clinic data, Outcome 1 Mean difference in SBP.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs Placebo: Clinic data

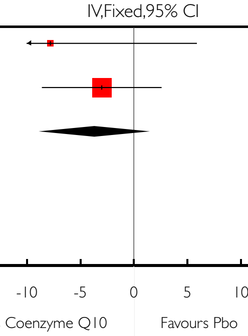
Outcome: 1 Mean difference in SBP

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Yamagami 1986	10	10	-7.8 (7)		14.2 %	-7.80 [-21.52, 5.92]
Young 2012	30	0	-3 (2.85)		85.8 %	-3.00 [-8.59, 2.59]
Total (95% CI)	**40**	**10**			**100.0 %**	**-3.68 [-8.86, 1.49]**

Heterogeneity: $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Coenzyme Q10 vs Placebo: Clinic data, Outcome 2 Mean difference in DBP.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs Placebo: Clinic data

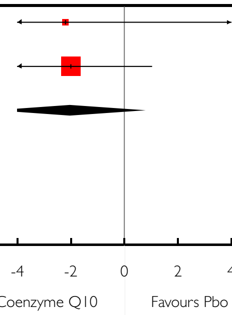
Outcome: 2 Mean difference in DBP

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Yamagami 1986	10	10	-2.2 (4)		13.1 %	-2.20 [-10.04, 5.64]
Young 2012	30	0	-2 (1.55)		86.9 %	-2.00 [-5.04, 1.04]
Total (95% CI)	**40**	**10**			**100.0 %**	**-2.03 [-4.86, 0.81]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Coenzyme Q10 vs Placebo: Clinic data, Outcome 3 Mean difference in HR.

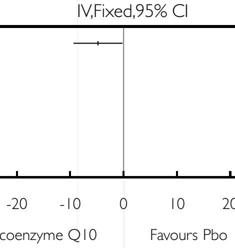
Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs Placebo: Clinic data

Outcome: 3 Mean difference in HR

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Young 2012	30	0	-4.8 (2.3)			-4.80 [-9.31, -0.29]

Test for subgroup differences: Not applicable



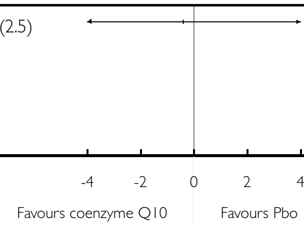
Analysis 2.1. Comparison 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements, Outcome 1 Mean Difference in SBP.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements

Outcome: 1 Mean Difference in SBP

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Young 2012	30	30	-0.4 (2.5)			-0.40 [-5.30, 4.50]
Test for subgroup differences: Not applicable						



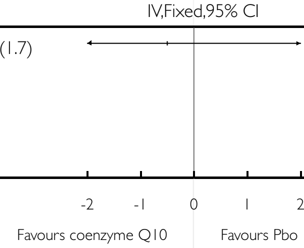
Analysis 2.2. Comparison 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements, Outcome 2 Mean Difference in DBP.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements

Outcome: 2 Mean Difference in DBP

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Young 2012	30	30	-0.5 (1.7)			-0.50 [-3.83, 2.83]
Test for subgroup differences: Not applicable						



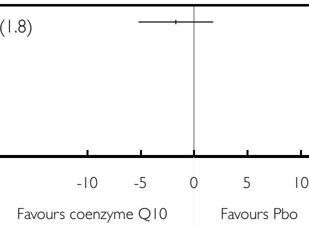
Analysis 2.3. Comparison 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements, Outcome 3 Mean Difference in HR.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 2 Coenzyme Q10 vs Placebo: 24 hr BP measurements

Outcome: 3 Mean Difference in HR

Study or subgroup	Coenzyme Q10 N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Young 2012	30	30	-1.7 (1.8)			-1.70 [-5.23, 1.83]
Test for subgroup differences: Not applicable						



APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 10 November 2015
----
1 ubiquinone.mp.
2 ((bioquinone or bio-quinone or coenzyme or co-enzyme or quinone) adj (q$ or “910”)).mp.
3 (coq10 or q10).mp.
4 (caomet or decorenone or mitocor or neuquinon$ or ubidecarenone or ubimaior or ubiquinol or ubiten).mp.
5 or/1-4
6 hypertension/
7 hypertens$.tw.
8 exp blood pressure/
9 (blood pressure or bloodpressure).mp.
10 or/6-9
11 randomized controlled trial.pt.
12 controlled clinical trial.pt.
13 randomi?ed.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 or/11-18

20 animals/ not (humans/ and animals/)
21 19 not 20
22 5 and 10 and 21

Appendix 2. Hypertension Group Specialised Register search strategy

Database: Hypertension Group Specialised Register <1946 to November 2015> via CRS
Search Date: 10 November 2015

#1 ((coenzyme q OR coq10 or q10 OR ubidecarenone OR ubiquinone)) AND ((RCT OR Review OR Meta-Analysis)):DE

Appendix 3. CENTRAL search strategy

Database: Cochrane Central Register of Controlled Trials <2015 Issue 10>
Search Date: 10 November 2015

ID Search
#1 (ubiquinone):ti,ab,kw
#2 ((bioquinone or bio-quinone or coenzyme or co-enzyme or quinone) near (q* or "910")):ti,ab,kw
#3 (caomet or coq10 or decorenone or mitocor or neuquinon$ or "q10" or ubidecarenone or ubimaior or ubiquinol or ubiten):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Hypertension] this term only
#6 hypertens*:ti,ab
#7 MeSH descriptor: [Blood Pressure] explode all trees
#8 ("blood pressure" or bloodpressure):ti,ab,kw
#9 #5 or #6 or #7 or #8
#10 #4 and #9

Appendix 4. EMBASE search strategy

Database: Embase <1974 to 2015 Week 46>
Search Date: 10 November 2015
----
1 ubidecarenone/
2 ((bioquinone or bio-quinone or coenzyme or co-enzyme or quinone) adj (q$ or "910")).mp.
3 (coq10 or q10).mp.
4 (caomet or decorenone or mitocor or neuquinon$ or ubimaior or ubiquinol or ubiquinone or ubiten).mp.
5 or/1-4
6 exp hypertension/
7 hypertens$.tw.
8 exp blood pressure/
9 (blood pressure or bloodpressure).mp.
10 or/6-9
11 randomized controlled trial/
12 crossover procedure/
13 double-blind procedure/
14 (randomi?ed or randomly).tw.
15 (crossover$ or cross-over$).tw.
16 placebo.ab.
17 (doubl$ adj blind$).tw.
18 assign$.ab.

19 allocat$.ab.
20 or/11-19
21 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
22 20 not 21
23 5 and 10 and 22

Appendix 5. CINAHL search strategy

Database: EBSCO CINAHL <1970 to November 2015>
Search Date: 10 November 2015

S23 S4 and S10 and S22
S22 (S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21)
S21 TI double blind* or AB double blind*
S20 AB groups
S19 TI trial or AB trial
S18 (MH "Quantitative Studies")
S17 TI placebo or AB placebo
S16 MH Placebos
S15 TI random* or AB random*
S14 (MH "Random Assignment")
S13 TI (clinic* n1 trial*) or AB (clinic* n1 trial*)
S12 PT Clinical trial
S11 (MH "Clinical Trials+")
S10 S5 OR S6 OR S7 OR S8 OR S9
S9 TX bloodpressure
S8 TX blood or arterial or diastolic or systolic N2 pressure
S7 (MH "Blood Pressure+")
S6 TI hypertens* or AB hypertens*
S5 (MH "Hypertension+")
S4 S1 OR S2 OR S3
S3 TX (caomet or coq10 or decorenone or mitocor or neuquinone or ubidecarenone or ubimaior or ubiquinol or ubiquinone or ubiten)
S2 TX (coenzyme q* or co-enzyme q* or coq10 or q10 or quinone q*)
S1 (MH "Coenzyme Q")

Appendix 6. Web of Science search strategy

Database: Web of Science (Science Citation Index Expanded and CPCI-Science)
Search Date: 10 November 2015
----
4 #3 AND #2 AND #1
3 TS=(randomized or randomised or randomly or control* or placebo* or double blind* or trial*)
2 TS=((hypertens* or bloodpressure or blood pressure or arterial pressure or diastolic pressure or systolic pressure))
1 TS=(caomet or coenzyme q or coenzyme q10 or co-enzyme q or co-enzyme q10 or coq10 or decorenone or mitocor or neuquinone or quinone or ubidecarenone or ubimaior or ubiquinone or ubiten)

WHAT'S NEW

Date	Event	Description
9 February 2016	New citation required and conclusions have changed	Updated searches: one new trial was found and one trial in the initial review was excluded Updated analyses and conclusions.
10 November 2015	New search has been performed	Updated searches.

CONTRIBUTIONS OF AUTHORS

James Wright and Meghan Ho jointly formulated the idea for the review, developed the basis for the protocol, interpreted the findings and wrote the final version of the review.

Meghan Ho took the lead role in searching, identifying and assessing studies, in data extraction and analyses, and in writing the first draft of the review.

Edmond Li assisted in identifying trials for the updated review and in interpretation of findings, independently assessed studies for inclusion, data extraction and risk of bias, as well as contributed to the figures, tables, and final draft of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics, Canada.

External sources

- Canadian Institutes of Health Research, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2009 version of this review, the study acceptance criteria was modified to "Participants must have a baseline blood pressure of at least 140 mmHg systolic or a diastolic blood pressure of at least 90 mmHg." In the 2008 protocol, the minimum systolic blood pressure required was 160 mmHg. The intervention was changed to "therapy with coenzyme Q10 compared to a placebo control, either as the sole antihypertensive therapy or added to current antihypertensive medication" from "monotherapy with coenzyme Q10 compared to a placebo" in the protocol.

In this first update of the review (2016), the following amendment to the intervention criteria was added: "current anti-hypertensive medication regimen that remains unchanged throughout the study."

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Bias; Blood Pressure [drug effects]; Diastole [drug effects]; Hypertension [*drug therapy]; Randomized Controlled Trials as Topic; Systole [drug effects]; Ubiquinone [*analogs & derivatives; deficiency; therapeutic use]

MeSH check words

Humans